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Dated 20 May 2003

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12AUG02 E740161-1 D00524
P01/7700 0.00-0218629.4

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1/77

## Request for grant of a patent

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| | | | |
|---|---|---|---|
| 1. | Your reference | **4-32610P1/HO 61** | |
| 2. | Patent application number *(The Patent Office will fill in this part)* | 09 AUG 2002 | 0218629.4 |
| 3. | Full name, address and postcode of the or of each applicant *(underline all surnames)* | **NOVARTIS AG**<br>**LICHTSTRASSE 35**<br>**4056 BASEL**<br>**SWITZERLAND** | |
| | Patent ADP number *(if you know it)* | | |
| | If the applicant is a corporate body, give the country/state of its incorporation | **SWITZERLAND** | 712748005 |
| 4. | Title of invention | **Organic Compounds** | |
| 5. | Name of your agent *(If you have one)* | | |
| | "Address for service" in the United Kingdom to which all correspondence should be sent *(including the postcode)* | **B.A. YORKE & CO.**<br>**CHARTERED PATENT AGENTS**<br>**COOMB HOUSE, 7 ST. JOHN'S ROAD**<br>**ISLEWORTH**<br>**MIDDLESEX TW7 6NH** | |
| | Patents ADP number *(if you know it)* | **1800001** | |

| | | | | |
|---|---|---|---|---|
| 6. | If you are declaring priority from one ore more earlier patent applications, give the country and the date of filing of the or of each of these earlier applications and *(if you know it)* the or each application number | Country | Priority application number *(if you know it)* | Date of filing (day/month/year) |
| 7. | If this application is divided or otherwise derived from an earlier UK application, give the number and the filing date of the earlier application | | Number of earlier application | Date of filing (day/month/year) |
| 8. | Is a statement of inventorship and of right to grant of a patent required in support of this request? *(Answer 'Yes' if:*<br>*a) any applicant named in part 3 is not an inventor, or*<br>*b) there is an inventor who is not named as an applicant, or*<br>*c) any named applicant is a corporate body.*<br>*(see note (d))* | **Yes** | | |

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| Continuation sheets of this form | |
| Description | 21 |
| Claim(s) | 3 |
| Abstract | |
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10. If you are also filing any of the following, state how many against each item.

| | |
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| Priority documents | |
| Translations of priority documents | |
| Statement of inventorship and right to grant of a patent *(Patents Form 7/77)* | |
| Request for preliminary examination and search *(Patents Form 9/77)* | ONE |
| Request for substantive examination *(Patents Form 10/77)* | |
| Any other documents *(please specify)* | |

11. I/We request the grant of a patent on the basis of this application

Signature B.A. Yorke & Co. Date **B.A. Yorke & Co.** **09 August 2002**

12. Name and daytime telephone number of person to contact in the United Kingdom

**Mrs. E. Cheetham**
**020 8560 5847**

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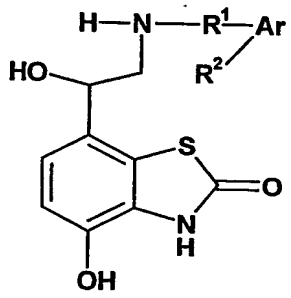
# Organic Compounds

This invention relates to organic compounds, their preparation and their use as pharmaceuticals.

In one aspect, the present invention provides compounds of formula I




I

in free or salt or solvate form, where

Ar denotes a phenylene group optionally substituted by one or more substituents selected from halogen, $C_1$-$C_8$-alkyl, $C_1$-$C_8$-alkoxy, $C_1$-$C_8$-alkoxy-$C_1$-$C_8$-alkyl, or $C_1$-$C_8$-alkoxy substituted by phenyl, $C_1$-$C_8$-alkyl-substituted phenyl or by $C_1$-$C_8$-alkoxy-substituted phenyl,

$R^1$ and $R^2$ are attached to adjacent carbon atoms in Ar, and

either $R^1$ is $C_1$-$C_8$-alkylene and $R^2$ is hydrogen, $C_1$-$C_8$-alkyl, $C_1$-$C_8$-alkoxy or halogen or $R^1$ and $R^2$ together with the carbon atoms in Ar to which they are attached denote a 5-, 6- or 7-membered cycloaliphatic ring.

"$C_1$-$C_8$-alkyl" as used herein denotes straight chain or branched $C_1$-$C_8$-alkyl, which may be, for example, methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, sec-butyl, tert-butyl, straight or branched pentyl, straight or branched hexyl, straight or branched heptyl, or straight or branched octyl. Preferably, $C_1$-$C_8$-alkyl is $C_1$-$C_4$-alkyl.

"$C_1$-$C_8$-alkoxy" as used herein denotes straight chain or branched $C_1$-$C_8$-alkoxy which may be, for example, methoxy, ethoxy, n-propoxy, isopropoxy, n-butoxy, isobutoxy, sec-butoxy, tert-butoxy, straight or branched pentoxy, straight or branched hexyloxy, straight or branched heptyloxy, or straight or branched octyloxy. Preferably, $C_1$-$C_8$-alkoxy is $C_1$-$C_4$-alkoxy.

"$C_1$-$C_8$-alkoxy-$C_1$-$C_8$-alkyl" as used herein denotes $C_1$-$C_8$-alkyl substituted by $C_1$-$C_8$-alkoxy. Preferably, $C_1$-$C_8$-alkoxy-$C_1$-$C_8$-alkyl is $C_1$-$C_4$-alkoxy- $C_1$-$C_4$-alkyl.

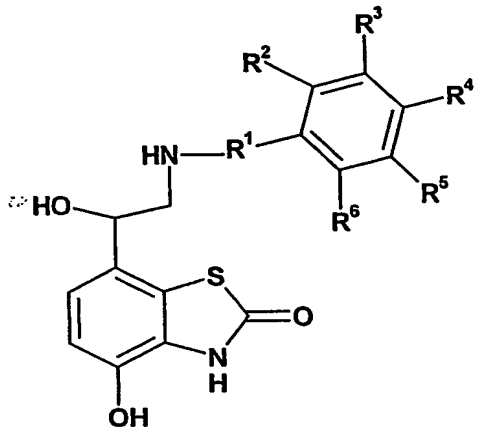
"Halogen" as used herein may be fluorine, chlorine, bromine or iodine; preferably it is fluorine, chlorine or bromine.

Ar may be, for example, phenylene which is unsubstituted or substituted by one or more substituents selected from halogen, $C_1$-$C_4$-alkyl, $C_1$-$C_4$-alkoxy, $C_1$-$C_4$-alkoxy-$C_1$-$C_4$-alkyl, or $C_1$-$C_4$-alkoxy substituted by phenyl, $C_1$-$C_4$-alkyl-substituted phenyl or by $C_1$-$C_4$-alkoxy-substituted phenyl. Preferably Ar is phenylene which is unsubstituted or substituted by one or two substituents selected from halogen, $C_1$-$C_4$-alkyl, $C_1$-$C_4$-alkoxy, or $C_1$-$C_4$-alkoxy substituted by phenyl. Preferably one substituent in Ar is para to $R^1$ and optional second and third substituents in Ar are meta to $R^1$.

$R^1$ as $C_1$-$C_8$-alkylene may be straight chain or branched $C_1$-$C_8$-alkylene, for example, methylene, ethylene, trimethylene, methylethylene, tetramethylene, $-CH(CH_3)CH_2CH_2-$, $-CH_2CH(CH_3)CH_2-$, pentylene, hexylene, heptylene or octylene, preferably $C_2$-$C_4$ alkylene, especially ethylene or methylethylene. $R^1$ and $R^2$ together with the carbon atoms to which they are attached as a cycloaliphatic ring may be, for example, a cyclopentane ring, optionally substituted by one or two $C_1$-$C_4$-alkyl groups, a cyclohexane ring, optionally substituted by one or two $C_1$-$C_4$-alkyl groups, or a cycloheptane ring, preferably a cyclopentane ring.

Preferred compounds of formula I in free or salt or solvate form include those where Ar is phenylene which is unsubstituted or substituted by one or two substituents selected from $C_1$-$C_4$-alkyl, $C_1$-$C_4$-alkoxy, or $C_1$-$C_4$-alkoxy substituted by phenyl, and either $R^1$ is $C_2$-$C_4$-alkylene and $R^2$ is hydrogen or $R^1$ and $R^2$ together with the carbon atoms to which they are attached in Ar denote a 5-membered cycloaliphatic ring.

More preferred compounds of formula I in free or salt or solvate form include those of formula



II

in free or salt or solvate form, where $R^1$ is $C_2$-$C_4$-alkylene and $R^2$ is hydrogen, or $R^1$ and $R^2$ together with the carbon atoms to which they are attached on the indicated benzene ring denote a 5-membered cycloaliphatic ring, $R^3$ and $R^6$ are each hydrogen, $R^4$ is hydrogen, $C_1$-$C_4$-alkyl, $C_1$-$C_4$-alkoxy or $C_1$-$C_4$-alkoxy substituted by phenyl and $R^5$ is hydrogen or $C_1$-$C_4$-alkyl.

Especially preferred compounds of formula I in free or salt or solvate form include those of formula II where $R^1$ is $C_2$-$C_3$-alkylene, $R^2$, $R^3$, $R^5$ and $R^6$ are each hydrogen, and $R^4$ is $C_1$-$C_4$-alkyl, $C_1$-$C_4$-alkoxy or $C_1$-$C_4$-alkoxy substituted by phenyl, and those where $R^1$ and $R^2$ together with the carbon atoms to which they are attached on the indicated benzene ring denote a cyclopentyl group fused to the benzene ring, $R^3$ and $R^6$ are each hydrogen and $R^4$ amd $R^5$ are each independently hydrogen or $C_1$-$C_4$-alkyl.

The compounds represented by formula I are capable of forming acid addition salts, particularly pharmaceutically acceptable acid addition salts. Pharmaceutically acceptable acid addition salts of the compounds of formula I include those of inorganic acids, for example, hydrohalic acids such as hydrofluoric acid, hydrochloric acid, hydrobromic acid or hydroiodic acid, nitric acid, sulfuric acid, phosphoric acid; and organic acids, for example aliphatic monocarboxylic acids such as formic acid, acetic acid, trifluoroacetic acid, propionic acid and butyric acid, aliphatic hydroxy acids such as lactic acid, citric acid, tartaric acid or malic acid, dicarboxylic acids such as maleic acid or succinic acid, aromatic carboxylic acids such as benzoic acid, p-chlorobenzoic acid, diphenylacetic acid or triphenylacetic acid, aromatic hydroxy acids such as o-hydroxybenzoic acid, p-hydroxybenzoic acid, 1-hydroxynaphthalene-2-carboxylic acid or 3-hydroxynaphthalene-2-carboxylic acid, and sulfonic acids such as methanesulfonic acid or benzenesulfonic acid.

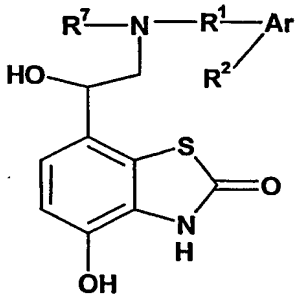
These salts may be prepared from compounds of formula I by known salt-forming procedures.

In formula I, the carbon atom alpha to the phenolic ring carries a hydroxy group and so is asymmetric, so the compounds exist in individual optically active isomeric forms or as mixtures thereof, e.g. as racemic or diastereomeric mixtures. The invention embraces both individual optically active R and S isomers as well as mixtures, e.g.racemic or diastereomeric mixtures, thereof.

Specific especially preferred compounds of formula I are those described hereinafter in the Examples.

The present invention also provides a process for the preparation of compounds of formula I in free or salt or solvate form which comprises

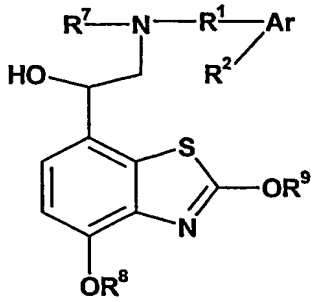
(i) either (A) reacting a compound of formula III



III

where Ar, $R^1$ and $R^2$ are as hereinbefore defined and $R^7$ denotes a protecting group, to replace $R^7$ by hydrogen or

(B) reacting a compound of formula IV



IV

where $R^1$, $R^2$ and $R^7$ are as hereinbefore defined and $R^8$ and $R^9$ each independently denote a protecting group, to convert groups $R^7$, $R^8$ and $R^9$ to hydrogen ; and

(ii) recovering the compound of formula I in free or salt or solvate form.

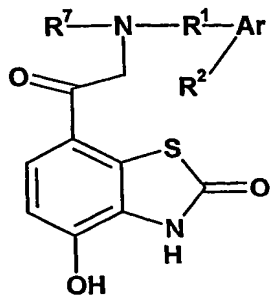
Where reference is made herein to protected functional groups or to protecting groups, the protecting groups may be chosen in accordance with the nature of the functional group, for example as described in Protective Groups in Organic Synthesis, T.W. Greene and P.G.M. Wuts, John Wiley & Sons Inc, Second Edition, 1991, which reference also describes procedures suitable for replacement of the protecting groups by hydrogen.

The protecting group $R^7$ may be, for example, a group chosen from known amine-protecting groups. Preferred protecting group $R^7$ include araliphatic groups, especially benzyl.

Protecting groups $R^8$ and $R^9$ may be chosen from known phenolic hydroxy – and alcoholic hydroxy-protecting groups respectively. Preferred groups $R^8$ and $R^9$ include $C_1$-$C_4$-alkyl groups, particularly branched groups such as isopropyl and tert-butyl.

Process variant (A) may be effected, for example, using known procedures for conversion of amine-protecting groups to hydrogen or analogous procedures. For example, where $R^7$ is a benzyl group it may be converted to hydrogen by catalytic hydrogenolysis of the compound of formula II, e.g. with a carboxylic acid such as formic acid, preferably in the presence of a palladium catalyst. This de-protection reaction may be carried out using procedures as described hereinafter in the Examples or analogous procedures.

Compounds of formula III may be prepared by reduction of a compound of formula V

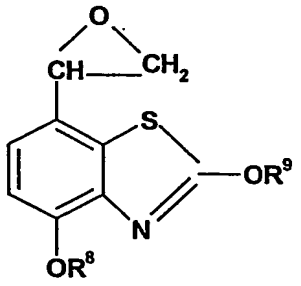



V

where Ar, $R^1$, $R^2$ and $R^7$ are as hereinbefore defined. The reduction may be effected using known methods for reduction of ketones to alcohols, or analogous methods. For example, the compounds of formula V may be reacted with $NaBH_4$ in an inert solvent such as an aliphatic alcohol. Suitable reaction temperatures are from -80°C to 100°C, conveniently from -5°C to 5°C. The reduction may be effected using known procedures or analogously as described hereinafter in the Examples.

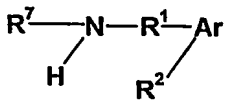
Process variant (B) may be effected using known procedures for conversion of hydroxy-protecting groups to hydrogen or analogous procedures. For example, where, $R^8$ and $R^9$ are alkyl groups, $R^8$ and $R^9$ may be converted to hydrogen by catalytic hydrogenolysis of the compounds of formula IV, e.g. with a carboxylic acid such as formic acid and a palladium catalyst, for example as hereinbefore described for conversion of $R^7$ to hydrogen, the resulting 2-hydroxybenzothiazole compound being in tautomeric equilibrium with the benzothiazol-2-one form.

Compounds of formula IV may be prepared by reacting a compound of formula VI



VI

where $R^8$ and $R^9$ are as hereinbefore defined, with a compound of formula

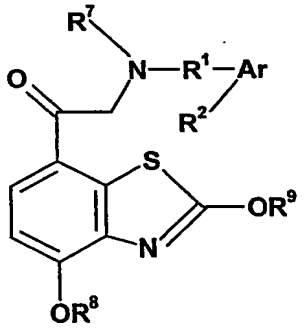


VII

where $R^1$, $R^2$ and $R^7$ are as hereinbefore defined. The reaction of compounds of formulae VI and VII may be effected using known procedures for epoxide-amine reactions or analogous procedures. The reaction is usually effected in an inert organic solvent, conveniently an alcohol such a n-butanol. Suitable reaction temperatures are, for example, from 0°C to

solvent reflux temperature. The reaction may be effected conveniently using a procedure as described hereinafter in the Examples, or analogously. Compounds of formula VI and VII may be prepared by known methods or analogously such as hereinafter described in the Examples.

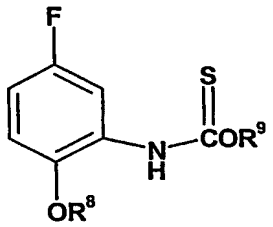
Compounds of formula V may be prepared by reacting a compound of formula



VIII

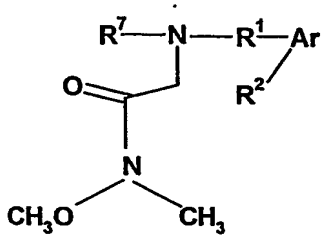
where $R^1$ , $R^2$, $R^7$ , $R^8$ and $R^9$ are as hereinbefore described, with concentrated hydrochloric or hydrobromic acid. The reaction is preferably carried out in an inert organic solvent such as an aliphatic alcohol.

Compounds of formula VIII may be prepared by reaction of a compound of formula



IX

where $R^8$ and $R^9$ are as hereinbefore defined, with a strong base, such as an alkyllithium, $NaNH_2$ or potassium tert-butoxide or a mixture of two or more thereof, and a compound of formula



X

where $R^1$, $R^2$ and $R^7$ are as hereinbefore defined. The reaction is preferably effected in an inert organic solvent, for example an ether such as tetrahydrofuran (THF). Suitable reaction temperatures may be, for example, from -80°C to 80°C. The reaction may be effected using a procedure as described hereinafter in the Examples or analogous procedures. Compounds of formulae IX and X may be prepared using known procedures or analogously, such as described hereinafter in the Examples.

Compounds of formula I in free or salt or solvate form are useful as pharmaceuticals. Accordingly the invention also provides a compound of formula I in free or salt form for use as a pharmaceutical. The compounds of formula I in free or salt form, hereinafter referred to alternatively as "agents of the invention", have good β2-adrenoreceptor agonist activity. The β2 agonist activity, onset of action and duration of action of the agents of the invention may be tested using the guinea pig tracheal stip in vitro assay according to the procedure of R.A. Coleman and A.T. Nials, J.Pharmacol. Methods (1989), 21(1), 71-86. The binding potency can be measured by a classical filtration binding assay according to the procedure of Current Protocols in Pharmacology (S.J.Enna(editor-in-chief) et al, John Wiley & Son, Inc, 1998), or by cAMP determination in cells expressing β2- adrenoceptor, according to the procedure of B. January et al, British J. Pharmacol. 123: 701-711 (1998). For example, the compounds of Examples 1, 3, 4 and 6 hereinbelow have Ki (β2) values of 0.3 nM, 1.6nM, 18.8nM and 6.6nM respectively.

The agents of the invention commonly have a rapid onset of action and have a prolonged stimulating action on the β2-adrenoreceptor, compounds of the Examples hereinbelow having durations of action of the order of up to 24 hours. The compounds of Examples 4 and 5 have T(50%) times (in minutes) of 403 and 326 respectively at 10nM concentration in the guinea pig tracheal strip assay, where T(50%) is the time for inhibition of contraction to decay to 50% of its maximum value.

Having regard to their β2 agonist activity, the agents of the invention are suitable for use in the treatment of any condition which is prevented or alleviated by activation of the β2-

adrenoreceptor. In view of their long acting β2 agonist activity, the agents of the invention are useful in the relaxation of bronchial smooth muscle and the relief of bronchoconstriction. Relief of bronchoconstriction can be measured in models such as the in vivo plethysmography models of Chong et al, J. Pharmacol.Toxicol. Methods 1998, 39, 163-168, Hammelmann et al, Am. J. Respir. Crit. Care Med., 1997, 156, 766-775 and analogous models. The agents of the invention are therefore useful in the treatment of obstructive or inflammatory airways diseases. In view of their long duration of action, it is possible to administer the agents of the invention once-a-day in the treatment of such diseases. In another aspect, agents of the invention commonly exhibit characteristics indicating a low incidence of side effects commonly encountered with β2 agonists such as tachycardia, tremor and restlessness, such agents accordingly being suitable for use in on demand (rescue) treatment as well as prophylactic treatment of obstructive or inflammatory airways diseases. The incidence of side effects may be determined, for example, as described by J.R.Fozard et al., Pulmonary Pharmacology & Therapeutics (2000) 14, 289-295.

Treatment of a disease in accordance with the invention may be symptomatic or prophylactic treatment. Inflammatory or obstructive airways diseases to which the present invention is applicable include asthma of whatever type or genesis including both intrinsic (non-allergic) asthma and extrinsic (allergic) asthma. Treatment of asthma is also to be understood as embracing treatment of subjects, e.g. of less than 4 or 5 years of age, exhibiting wheezing symptoms and diagnosed or diagnosable as "wheezy infants", an established patient category of major medical concern and now often identified as incipient or early-phase asthmatics. (For convenience this particular asthmatic condition is referred to as "wheezy-infant syndrome".)

Prophylactic efficacy in the treatment of asthma will be evidenced by reduced frequency or severity of symptomatic attack, e.g. of acute asthmatic or bronchoconstrictor attack, improvement in lung function or improved airways hyperreactivity. It may further be evidenced by reduced requirement for other, symptomatic therapy, i.e. therapy for or intended to restrict or abort symptomatic attack when it occurs, for example anti-inflammatory (e.g. corticosteroid) or bronchodilatory. Prophylactic benefit in asthma may in particular be apparent in subjects prone to "morning dipping". "Morning dipping" is a recognised asthmatic syndrome, common to a substantial percentage of asthmatics and characterised by asthma attack, e.g. between the hours of about 4 to 6 am, i.e. at a time

normally substantially distant form any previously administered symptomatic asthma therapy.

Other inflammatory or obstructive airways diseases and conditions to which the present invention is applicable include acute lung injury (ALI), adult/acute respiratory distress syndrome (ARDS), chronic obstructive pulmonary, airways or lung disease (COPD, COAD or COLD), including chronic bronchitis, or dyspnea associated therewith, emphysema, as well as exacerbation of airways hyperreactivity consequent to other drug therapy, in particular other inhaled drug therapy. The invention is also applicable to the treatment of bronchitis of whatever type or genesis including, e.g., acute, arachidic, catarrhal, croupus, chronic or phthinoid bronchitis. Further inflammatory or obstructive airways diseases to which the present invention is applicable include pneumoconiosis (an inflammatory, commonly occupational, disease of the lungs, frequently accompanied by airways obstruction, whether chronic or acute, and occasioned by repeated inhalation of dusts) of whatever type or genesis, including, for example, aluminosis, anthracosis, asbestosis, chalicosis, ptilosis, siderosis, silicosis, tabacosis and byssinosis.

Having regard to their β2 agonist activity, the agents of the invention are also useful in the treatment of a condition requiring relaxation of smooth muscle of the uterus or vascular system. They are thus useful for the prevention or alleviation of premature labour pains in pregnancy. They are also useful in the treatment of chronic and acute urticaria, psoriasis, rhinitis, allergic conjunctivitis, actinitis, hay fever, and mastocytosis.

The agents of the invention are also useful as co-therapeutic agents for use in combination with other drug substances such as anti-inflammatory, bronchodilatory or antihistamine drug substances, particularly in the treatment of obstructive or inflammatory airways diseases such as those mentioned hereinbefore, for example as potentiators of therapeutic activity of such drugs or as a means of reducing required dosaging or potential side effects of such drugs. An agent of the invention may be mixed with the other drug substance in a fixed pharmaceutical composition or it may be administered separately, before, simultaneously with or after the other drug substance. Such anti-inflammatory drugs include steroids, in particular glucocorticosteroids such as budesonide, beclamethasone, fluticasone, ciclesonide or mometasone, LTB4 antagonists such as those described in US5451700, LTD4 antagonists such as montelukast and zafirlukast, dopamine receptor agonists such as cabergoline, bromocriptine, ropinirole and 4-hydroxy-7-[2-[[2-[[3-(2-phenylethoxy)propyl]sulfonyl]ethyl]-

amino]ethyl]-2(3H)-benzothiazolone and pharmaceutically acceptable salts thereof (the hydrochloride being Viozan® - AstraZeneca), and PDE4 inhibitors such as Ariflo® (GlaxoSmith Kline), Roflumilast (Byk Gulden),V-11294A (Napp), BAY19-8004 (Bayer), SCH-351591 (Schering-Plough), and PD189659 (Parke-Davis). Such bronchodilatory drugs include anticholinergic or antimuscarinic agents, in particular ipratropium bromide, oxitropium bromide and tiotropium bromide. Co-therapeutic antihistamine drug substances include cetirizine hydrochloride, acetaminophen, clemastine fumarate, promethazine, loratidine, desloratidine, diphenhydramine and fexofenadine hydrochloride. Combinations of agents of the invention and steroids, beta-2 agonists, PDE4 inhibitors or LTD4 antagonists may be used, for example, in the treatment of COPD or, particularly, asthma. Combinations of agents of the invention and anticholinergic or antimuscarinic agents, PDE4 inhibitors, dopamine receptor agonists or LTB4 antagonists may be used, for example, in the treatment of asthma or, particularly, COPD.

In accordance with the foregoing, the present invention also provides a method for the treatment of an obstructive or inflammatory airways disease which comprises administering to a subject, particularly a human subject, in need thereof an effective amount a compound of formula I, or a pharmaceutically acceptable salt thereof, as hereinbefore described. In another aspect, the invention provides a compound of formula I, or a pharmaceutically acceptable salt thereof, as hereinbefore described for use in the preparation of a medicament for the treatment of an obstructive or inflammatory airways disease.

The agents of the invention may be administered by any appropriate route, e.g. orally, for example in the form of a tablet or capsule; parenterally, for example intravenously; topically to the skin, for example in the treatment of psoriasis; intranasally, for example in the treatment of hay fever; or, preferably, by inhalation, particularly in the treatment of obstructive or inflammatory airways diseases.

In a further aspect, the invention also provides a pharmaceutical composition comprising as active ingredient a compound of formula I in free form or in the form of a pharmaceutically acceptable salt or solvate thereof, optionally together with a pharmaceutically acceptable diluent or carrier therefor. Such compositions may be prepared using conventional diluents or excipients and techniques known in the galenic art. Thus oral dosage forms may include tablets and capsules. Formulations for topical administration may take the form of creams, ointments, gels or transdermal delivery systems, e.g. patches. Compositions for inhalation

may comprise aerosol or other atomizable formulations, e.g. an aerosol comprising a dispersion of the agent of the invention in a fluorine-substituted hydrocarbon, e.g. a HFA such as HFA134a or HFA227, or dry powder formulations.

The invention also includes (A) a compound of formula I as hereinbefore described in free form, or a pharmaceutically acceptable salt or solvate thereof, in inhalable form; (B) an inhalable medicament comprising such a compound in inhalable form together with a pharmaceutically acceptable carrier in inhalable form; (C) a pharmaceutical product comprising such a compound in inhalable form in association with an inhalation device; and (D) an inhalation device containing such a compound in inhalable form.

Dosages employed in practising the invention will of course vary depending, for example, on the particular condition to be treated, the effect desired and the mode of administration. In general, suitable daily dosages for administration by inhalation are of the order of from 1 to 5000μg.

The invention is illustrated by the following Examples. Compounds used in preparing the compounds of the Examples are prepared as follows:

Preparation 1- [4-(4-phenyl-butoxy)-phenyl]-acetonitrile

1-Chloro-4-phenylbutane is added to a suspension of 4-hydroxyphenylacetonitrile (1.91 g), $K_2CO_3$ (4.64 g) and sodium iodide (600 mg) in acetonitrile (30 ml) and refluxed for 68 hours. Filtration, evaporation followed by silica gel flash column chromatography, eluent 4:1 hexane: $CH_3CO_2CH_2CH_3$, gives the title compound.

$^1$H nmr ($d_6$-DMSO, 400 MHz); 7.30-7.13 (m, 7H), 6.95-6.87 (m, 2H), 3.97 (t, J = 6 Hz, 2H), 3.92 (s, 2H), 2.62 (t, J = 7 Hz, 2H), 1.77-1.63 (m, 4H).

Preparation 2- 2-[4-(4-phenyl-butoxy)-phenyl]-ethylamine

The title compound (395 mg) is prepared from [4-(4-phenyl-butoxy)-phenyl]-acetonitrile (500 mg) by the procedure of B. Staskun et al J. Chem Soc. (C) 1966, 531.

$^1$H nmr ($d_6$-DMSO, 400 MHz); 7.32-7.10 (m, 5H), 7.10-7.00 (m, 2H), 6.83-6.75 (m, 2H), 3.97-3.80 (m, 2H), 3.70-2.87 (br s, 2H), 2.73-2.45 (m, 6H), 1.77-1.60 (m, 4H).

Preparation 3 - benzyl-{2-[4-(4-phenyl-butoxy)-phenyl]-ethyl}-amine

The title compound (2.1 g) is prepared from 2-[4-(4-phenyl-butoxy)-phenyl]-ethylamine by the procedure of A. F. Abdel-Magid J. Org. Chem. 1996, 61, 3849. MS (ES+) 361.

Preparation 4 - (benzyl-{2-[4-(4-phenyl-butoxy)-phenyl]-ethyl}-amino)-acetic acid tert-butyl ester

Butyl bromoacetate (4.94 ml) is added to a solution of benzyl-{2-[4-(4-phenyl-butoxy)-phenyl]-ethyl}-amine (10 g) and N,N-diisopropylethylamine (10.2 ml) in tetrahydrofuran (40 ml) at 0°C. After 18 hours at room temperature the reaction mixture is partitioned between aqueous $NaHCO_3$ and $CH_3CO_2CH_2CH_3$, followed by evaporation of the $CH_3CO_2CH_2CH_3$ layers and silica gel column chromatography, eluent 9:1 hexane:$CH_3CO_2CH_2CH_3$, to give the title compound. MS (ES+) 474.

Preparation 5 - tert-butoxy-5-fluoro-phenylamine

A suspension of platinum oxide (17 g) in a solution of 1-tert-butoxy-4-fluoro-2-nitro-benzene (22.5 g, prepared by procedure T. F. Woiwode et al J. Org. Chem. 1998, 63, 9594.) in $CH_3OH$ (1.5 l) is stirred under an atmosphere of hydrogen for 18 hours. Filtration through Celite and evaporation gives the title compound. $^{19}F$ nmr ($CDCl_3$, 376 MHz); -43.4.

Preparation 6 - (benzyl-{2-[4-(4-phenyl-butoxy)-phenyl]-ethyl}-amino)-acetic acid

A solution of (benzyl-{2-[4-(4-phenyl-butoxy)-phenyl]-ethyl}-amino)-acetic acid tert-butyl ester (12.1 g) in $CH_2Cl_2$ (50 ml) and $CF_3CO_2H$ (30 ml) is stirred for 18 hours at room temperature after which evaporation gives the title compound. MS (ES+) 418.

Preparation 7 - 1-tert-butoxy-4-fluoro-2-isothiocyanato-benzene

Carbon disulphide (38.6 ml) is added to a solution of 2-tert-butoxy-5-fluoro-phenylamine (58.8 g) and triethylamine (89.5 ml) in toluene (66 ml) and the reaction mixture stirred at room temperature for 18 hours, then evaporated. Chloroform (200ml) and triethylamine (44.9 ml) are added to the residue, which is cooled before the addition of ethyl chloroformate (30.8 ml). After 15 minutes at 0°C, the reaction mixture is washed sequentially with aqueous 3N HCl, saturated brine, saturated $NaHCO_3$ and saturated brine, then evaporated to give the title compound.

$^1H$ nmr ($CDCl_3$, 400 MHz); 7.10-7.03 (m, 1H), 6.93-6.87 (m, 1H), 6.86-6.80 (m, 1H), 1.43 (s, 9H).

Preparation 8 – 2-(benzyl-{2-[4-(4-phenyl-butoxy)-phenyl]-ethyl}-amino)-N-methoxy-N-methyl-acetamide

1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (5.30 g) is added to a solution of (benzyl-{2-[4-(4-phenyl-butoxy)-phenyl]-ethyl}-amino)-acetic acid (12.56 g), N,N-dimethylaminopyridine (3.38 g), N,O-dimethylhydroxylamine (8.09 g) and N-methylmorpholine (6.08 ml) in tetrahydrofuran (150 ml). After refluxing for 4 hours, the reaction mixture is partitioned between water and $CH_3CO_2CH_2CH_3$. Evaporation of the $CH_3CO_2CH_2CH_3$ layers and silica gel column chromatography, eluent 9:1 hexane: $CH_3CO_2CH_2CH_3$, gives the title compound. MS (ES+) 461.

Preparation 9 - (2-tert-butoxy-5-fluoro-phenyl)-thiocarbamic acid O-isopropyl ester

A solution of 1-tert-butoxy-4-fluoro-2-isothiocyanato-benzene (50.0 g) and triethylamine (31 ml) in isopropanol (170 ml) is refluxed for 48 hours. Evaporation of the reaction mixture followed by silica gel flash column chromatography, eluent 20:1 hexane: $CH_3CO_2CH_2CH_3$ gives the title compound.

$^1H$ nmr ($CDCl_3$, 400 MHz); 8.60 (br s, 1H), 7.38 (br s, 1H), 7.50-6.87 (m, 1H), 6.67-6.58 (m, 1H), 5.64-5.50 (m, 1H), 1.43-1.32 (m, 6H), 1.32-1.25 (s, 9H).

Preparation 10 - 2-(benzyl-{2-[4-(4-phenyl-butoxy)-phenyl]-ethyl}-amino)-1-(4-tert-butoxy-2-isopropoxy-benzothiazol-7-yl)-ethanone

A solution of tert.butyl lithium in pentane (12.3 ml, 1.7 M) is added to a solution of (2-tert-butoxy-5-fluoro-phenyl)-thiocarbamic acid O-isopropyl ester (3.20 g) in tetrahydrofuran (10 ml) at –78°C, the solution warmed to –20°C over 1 hour then re-cooled –78°C and a solution of 2-(benzyl-{2-[4-(4-phenyl-butoxy)-phenyl]-ethyl}-amino)-N-methoxy-N-methyl-acetamide QAF203 in tetrahydrofuran (10 ml) added at –78°C. The reaction mixture is warmed to room temperature and partitioned between aqueous $NH_4Cl$ and $CH_3CO_2CH_2CH_3$. Evaporation of the $CH_3CO_2CH_2CH_3$ layers and silica gel column chromatography, eluent 4:1 hexane: $CH_3CO_2CH_2CH_3$, gives the title compound. MS (ES+) 665.

Preparation 11 - 7-[(benzyl-{2-[4-(4-phenyl-butoxy)-phenyl]-ethyl}-amino)-acetyl]-4-hydroxy-3H-benzothiazol-2-one

A solution of 2-(benzyl-{2-[4-(4-phenyl-butoxy)-phenyl]-ethyl}-amino)-1-(4-tert-butoxy-2-isopropoxy-benzothiazol-7-yl)-ethanone (2.49 g) in isopropanol (20 ml) and conc. hydrobromic acid (20 ml) is heated at 50°C. After 3 hours the reaction mixture is partitioned between $CH_3CO_2CH_2CH_3$ and water, and the $CH_3CO_2CH_2CH_3$ layer washed with aqueous

$NaHICO_3$ then brine. Evaporation of the $CH_3CO_2CH_2CH_3$ layers and silica gel column chromatography, eluent 4:1 hexane: $CH_3CO_2CH_2CH_3$, gives the title compound. MS (ES+) 567.

Preparation 12 - 7-[2-(benzyl-{2-[4-(4-phenyl-butoxy)-phenyl]-ethyl}-amino)-1-hydroxy-ethyl]-4-hydroxy-3H-benzothiazol-2-one

$NaBH_4$ (2.67 g) is added portion-wise to a solution of 7-[(benzyl-{2-[4-(4-phenyl-butoxy)-phenyl]-ethyl}-amino)-acetyl]-4-hydroxy-3H-benzothiazol-2-one (0.40 g) in $CH_3OH$ (15 ml) at 0°C. After 30 minutes the reaction mixture is partitioned between $CH_3CO_2CH_2CH_3$ and water. Evaporation of the $CH_3CO_2CH_2CH_3$ layers and silica gel column chromatography, eluent 1:1 hexane: $CH_3CO_2CH_2CH_3$, gives the title compound. MS (ES+) 569.

Preparation 13 - benzyl-indan-2-ylamine

The title compound is prepared from indan-2-one by the procedure of A. F. Abdel-Magid et al J. Org. Chem. 1996, 61, 3849. MS (ES+) 224.

Preparation 14 - 2-(benzyl-indan-2-yl-amino)-N-methoxy-N-methyl-acetamide

The title compound is prepared from benzyl-indan-2-ylamine by procedures analogous to those of Preparations 4, 6 and 8. MS (ES+) 326.

Preparation 15 – 7-[2-(benzyl-{2-indan-2-yl}amino)-1-hydroxyethyl]-4-hydroxy-3H-benzothiazolone

The title compound is prepared from 2-(benzyl-indan-2-yl-amino)-N-methoxy-N-methyl-acetamide and (2-tert-butoxy-5-fluoro-phenyl)-thiocarbamic acid O-isopropyl ester using procedures analogous to those of Preparations 10, 11 and 12.

Preparation 16 - 2-[benzyl-(5,6-diethyl-indan-2-yl)-amino]-N-methoxy-N-methyl-acetamide

The title compound is prepared from 5,6-diethyl-indan-2-ylamine (prepared by the procedure of WO 0075114) by procedures analogous to those of Preparations 3, 4, 6 and 8.
MS (ES+) 382.

Preparation 17 - 2-{benzyl-[(R)-2-(4-methoxy-phenyl)-1-methyl-ethyl]-amino}-N-methoxy-N-methyl-acetamide

The title compound Is prepared from (R)-2-(4-methoxy-phenyl)-1-methyl-ethylamine (R. Hett et al Tetrahedron Lett. 1997, 38, 1125.) by procedures analogous to those of Preparations 3, 4, 6 and 8. MS (ES+) 358.

Preparation 18 - 2,2,2-trifluoro-N-phenethyl-acetamide

Trifluoroacetic anhydride (64.5 ml) is added dropwise to a solution of phenethylamine (52 ml) and triethylamine (58 ml) in $CH_2Cl_2$ at 0°C. After 18 hours at room temperature the reaction mixture is washed with aqueous citric acid, brine and aqueous $NaHCO_3$, dried with $MgSO_4$ and evaporated to give the title compound.

Preparation 19 - 2,2,2-trifluoro-N-[2-(4-isobutyryl-phenyl)-ethyl]-acetamide

Isobutryl chloride (19.7 ml) is added dropwise to a mixture of 2,2,2-trifluoro-N-phenethyl-acetamide (34.2 g) and aluminium chloride (48.2 g) in $CH_2Cl_2$ (450 ml) at 0°C. After 18 hours at room temperature the reaction mixture is poured onto ice (2000 g), extracted 3 times with $CH_2Cl_2$, dried with $MgSO_4$ and evaporated to give the title compound which is used without further purification.

Preparation 20 - 2,2,2-trifluoro-N-[2-(4-isobutyl-phenyl)-ethyl]-acetamide

A solution of 2,2,2-trifluoro-N-[2-(4-isobutyryl-phenyl)-ethyl]-acetamide (19.4 g) in ethanol (200 ml) and conc. hydrochloric acid (5 ml) is stirred for 23 hours under 1 atmosphere of hydrogen over a palladium on carbon catalyst (1.9 g). Filtration, evaporation and purification by silica gel chromatography, eluting with chloroform, gives the title compound.
$^{13}C$ nmr ($CDCl_3$, 101 MHz); 157.55, 140.90, 135.10, 130.03, 128.78, 45.40, 41.46, 34.94, 30.61, 22.72.

Preparation 21 - 2-(4-isobutyl-phenyl)-ethylamine

Potassium carbonate (18.5 g) is added to a solution of 2,2,2-trifluoro-N-[2-(4-isobutyl-phenyl)-ethyl]-acetamide (12.2 g) in methanol (45 ml) and water (19 ml) at room temperature. The mixture is heated at 45°C for 8 hours. Dilution with water (200 ml), extraction with dichloromethane, drying over magnesium sulphate and evaporation gives the title compound.
$^{13}C$ nmr ($CDCl_3$, 101 MHz); 140.10, 137.40, 129.56, 128.94, 45.45, 43.99, 40.01, 30.45, 22.79.

Preparation 22 - {benzyl-[2-(4-isobutyl-phenyl)-ethyl]-amino}-acetic acid

The title compound is prepared from 2-(4-isobutyl-phenyl)-ethylamine by procedures analogous to those of Preparations 3, 4 and 6. MS (ES+) 326.

Preparation 23 - 2-{benzyl-[2-(4-isobutyl-phenyl)-ethyl]-amino}-N-methoxy-N-methyl-acetamide

Isobutyl chloroformate (0.54 ml) is added to a solution of {benzyl-[2-(4-isobutyl-phenyl)-ethyl]-amino}-acetic acid (1.5 g) and Hunig's base (3.61 ml) in dichloromethane (21 ml) at 0°C. After 2 hours N,O-dimethylhydroxylamine hydrochloride (0.49 g) is added, the reaction stirred a further 30 minutes at 0°C then partitioned between aqueous $NaHCO_3$ and $CH_2Cl_2$, dried over $MgSO_4$, evaporated and purified by silica gel chromatography, eluting with 10% ethyl acetate in $CH_2Cl_2$, to give the title compound. MS (ES+) 370.

Preparation 24 – 2-{benzyl-[2-(4-propyl-phenyl)-ethyl]-amino}-N-methoxy-N-methyl-acetamide

The title compound is prepared from 2,2,2-trifluoro-N-phenethyl-acetamide by procedures analogous to those of Preparations 19, 20, 21, 3, 4, 6 and 22. MS (ES+) 356 (96%), 266.

Preparation 25 – N-benzyl-2-(4-bromo-phenyl)-acetamide

4-Bromophenylacetic acid (23.24 g) is dissolved in dichloromethane (400 ml). 1-(3-Dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (20.70 g) is added followed by DMAP (0.13 g) and the reaction mixture stirred at room temperature for 10 minutes. Benzylamine (12.14 g), dissolved in dichloromethane (100 ml), is then slowly added and the reaction mixture stirred at room temperature. After 1 hour the reaction is shown to be complete by TLC. The reaction mixture is washed with 1M HCl (3 x 200 ml), water (3 x 200 ml) and brine (200 ml). The organic layer dried is over $MgSO_4$, filtered and the solvent removed *in vacuo*. The title compound is obtained following crystallisation from ethylacetate. MS (ES+) *m/e* 304 ($MH^+ - Br^{79}$) and 306 ($MH^+ - Br^{81}$).

Preparation 26 - N-benzyl-2-(4-propyl-phenyl)-acetamide

1,1'-Bis(diphenylphosphino)ferrocenedichloro palladium(II) (0.39 g) is placed in a flask under an atmosphere of argon. The flask is cooled to –78°C and then propylzinc bromide (200 ml, 0.5M in THF) is slowly added. N-Benzyl-2-(4-bromo-phenyl)-acetamide (14.48g, 47.62mmol), dissolved in THF (500 ml), is then slowly added and the reaction mixture stirred at room temperature. After 24 hours further propylzinc bromide (10 ml, 0.5M in THF) is added and the reaction mixture stirred at room temperature. The reaction is shown to be complete by TLC after 24 hours and is quenched by the addition of 2M HCl (50 ml) and then 80-90% of the solvent is removed *in vacuo*. The residue is partitioned between ethyl

acetate (250 ml) and water (250 ml). The organic layer is washed with water (250 ml) and brine (250 ml), dried over $MgSO_4$, filtered and the solvent removed *in vacuo*. Recrystallisation from cyclohexane gives the title compound. MS (ES+) *m/e* 268 ($MH^+$).

Preparation 27 - benzyl-[2-(4-propyl-phenyl)-ethyl]-amine hydrochloride

DIBAL (47.5 ml, 1.5M in toluene) is slowly added to N-benzyl-2-(4-propyl-phenyl)-acetamide (9.50 g) in toluene (200 ml) cooled on an ice-bath. The reaction mixture is stirred at room temperature until shown to be complete by TLC. The reaction mixture is recooled on an ice-bath and quenched by the addition of water (10 ml), washed further with water (2 x 100 ml) and brine (100 ml), dried over $MgSO_4$, filtered and the solvent removed *in vacuo*. The residue is taken up in hexane : ethylacetate (5 :1) (100 mL) and any insoluble material is filtered off. The solvent is removed *in vacuo* and the residue dissolved in $Et_2O$. 1M HCl in $Et_2O$ (30ml) is added and the title compound obtained by filtration. MS (ES+) *m/e* 254 ($MH^+$).

Preparation 28 - 1-(4-tert.butoxy-2-isopropoxy-benzothiazol-7-yl)-2-chloro-ethanone

tert.Butyllithium (22.7 ml, 1.7M in pentane) is added dropwise to a solution of (2-tert.butoxy-5-fluoro-phenyl)-thiocarbamic acid O-isopropyl ester (5.00 g) in THF (20 ml) at –78°C. This solution is then allowed to warm to –20°C and a dried mixture of lithium chloride (2.12 g) and copper (I) cyanide (2.24 g) in THF (50 mL) is added. After 15 minutes chloroacetyl chloride (4.36 g) is added and the reaction mixture allowed to warm to 0°C. This temperature is maintained for 1 hour and then the reaction mixture is quenched by the addition of saturated aqueous $NH_4Cl$ (5 ml). The reaction mixture is partitioned between ethyl acetate (250 ml) and water (250 ml). The organic layer is washed with water (250 ml) and brine (250 ml), dried over $MgSO_4$, filtered and the solvent removed *in vacuo*. The title compound is obtained by flash column chromatography (silica, iso-hexane / ethyl acetate 10:1). MS (ES+) *m/e* 341 ($M^+$).

Preparation 29 - (R)-1-(4-tert-butoxy-2-isopropoxy-benzothiazol-7-yl)-2-chloro-ethanol

Borane-THF complex, (14.64 ml, 1M in THF) is added dropwise to a solution of (1R, 2S)-(+)-1-amino-2-indanol (0.22 g) in THF (50 ml) and the solution is stirred at room temperature for 15 minutes. A solution of 1-(4-tert.butoxy-2-isopropoxy-benzothiazol-7-yl)-2-chloro-ethanone (5.00 g) in THF (50 mL) is then added dropwise over a period of 1 hour. The reaction mixture is stirred at room temperature for a further 15 minutes and then quenched by the addition of 0.2M $H_2SO_4$ (5 ml). The reaction mixture is partitioned between

ethyl acetate (200 ml) and 0.2M $H_2SO_4$ (200 mL). The organic layer is washed with water (200 ml) and brine (200 ml), dried over $MgSO_4$, filtered and the solvent removed *in vacuo* to give the title compound. MS (ES+) *m/e* 344 ($MH^+$).

Preparation 30 - 4-tert.butoxy-2-isopropoxy-7-(R)-oxiranyl-benzothiazole

A mixture of (R)-1-(4-tert.butoxy-2-isopropoxy-benzothiazol-7-yl)-2-chloro-ethanol (4.70 g) and potassium carbonate (7.48 g) in acetone (250 ml) is refluxed for 48 hours. The reaction mixture is allowed to cool, filtered and the solvent removed *in vacuo* to give the title compound. MS (ES+) *m/e* 308 ($MH^+$).

Preparation 31 - (R)-2-{benzyl-[2-(4-propyl-phenyl)-ethyl]-amino}-1-(4-tert-butoxy-2-isopropoxy-benzothiazol-7-yl)-ethanol

A solution of 4-tert.butoxy-2-isopropoxy-7-(R)-oxiranyl-benzothiazole (3.50 g) and benzyl-[2-(4-propyl-phenyl)-ethyl]-amine (3.03 g) in 1-butanol (25 ml) is stirred at 110°C. The reaction is shown to be complete by TLC after 18 hours.The title compound is obtained after purification by flash column chromatography (silica, iso-hexane / ethyl acetate 10:1).
MS (ES+) *m/e* 561 ($MH^+$).

Preparation 32 - (S)-1-(4-tert-butoxy-2-isopropoxy-benzothiazol-7-yl)-2-chloro-ethanol

The title compound is prepared by a procedure analogous to that of Preparation 29 using Borane-THF complex, (14.64 ml, 1M in THF), (1S, 2R)-(-)-1-amino-2-indanol (0.22 g) and 1-(4-tert.butoxy-2-isopropoxy-benzothiazol-7-yl)-2-chloro-ethanone (5.00 g).
MS (ES+) *m/e* 344 ($MH^+$).

Example 1 - 4-hydroxy-7-(1-hydroxy-2-{2-[4-(4-phenyl-butoxy)-phenyl]-ethylamino}-ethyl)-3H-benzothiazol-2-one

Palladium black (0.2 g) is added portion-wise to a solution of 7-[2-(benzyl-{2-[4-(4-phenyl-butoxy)-phenyl]-ethyl}-amino)-1-hydroxy-ethyl]-4-hydroxy-3H-benzothiazol-2-one (0.29 g) in formic acid (10 ml) at room temperature. After 1 hour the catalyst is removed by filtration and the filtrate partitioned between $CH_3CO_2CH_2CH_3$ and aqueous $NaHCO_3$ . Evaporation of the $CH_3CO_2CH_2CH_3$ layers and recrystallisation from hexane / $CH_3CO_2CH_2CH_3$ gives the title compound. MS (ES+) 479.

Example 2 - 4-hydroxy-7-[1-hydroxy-2-(indan-2-ylamino)-ethyl]-3H-benzothiazol-2-one

This compound is prepared from the product of Preparation 15 by a procedure analogous to that of Example 1. MS (ES+) 343.

Example 3 - 4-hydroxy-7-{1-hydroxy-2-[(R)-2-(4-methoxy-phenyl)-1-methyl-ethylamino]-ethyl}-3H-benzothiazol-2-one

The title compound is prepared from 2-{benzyl-[(R)-2-(4-methoxy-phenyl)-1-methyl-ethyl]-amino}-N-methoxy-N-methyl-acetamide and (2-tert-butoxy-5-fluoro-phenyl)-thiocarbamic acid O-isopropyl by following procedures analogous to those of Preparations 10, 11 and 12 and Example 1. MS (ES+) 375.

Example 4 - 4-hydroxy-7-{1-hydroxy-2-[2-(4-isobutyl-phenyl)-ethylamino]-ethyl}-3H-benzothiazol-2-one

The title compound is prepared from 2-{benzyl-[2-(4-isobutyl-phenyl)-ethyl]-amino}-N-methoxy-N-methyl-acetamide and (2-tert-butoxy-5-fluoro-phenyl)-thiocarbamic acid O-isopropyl ester by procedures analogous to those of Preparations 10, 11 and 12 and Example 1. MS (ES+) 387.

Example 5 - 4-hydroxy-7-{1-hydroxy-2-[2-(4-propyl-phenyl)-ethylamino]-ethyl}-3H-benzothiazol-2-one

The title compound is prepared from 2-{benzyl-[2-(4-isobutyl-phenyl)-ethyl]-amino}-N-methoxy-N-methyl-acetamide and (2-tert-butoxy-5-fluoro-phenyl)-thiocarbamic acid O-isopropyl ester by procedures analogous to those of Preparations 10, 11 and 12 and Example 1.

$^1$H nmr (MeOH-$d_4$, 400 MHz); 7.16-6.97 (m, 4H), 6.86 (d, 1H, $J$ = 8 Hz), 6.65 (d, 1H, $J$ = 8 Hz), 4.87-4.85 (m, 1H), 3.20-3.12 (m, 2H), 3.10-3.02 (m, 2H), 2.89-2.87 (m, 2H), 2.49-2.44 (m, 2H), 1.57-1.46 (m, 2H), 0.84-0.79 (m, 3H).

Example 6 - 4-hydroxy-7-{(R)-1-hydroxy-2-[2-(4-propyl-phenyl)-ethylamino]-ethyl}-3H-benzothiazol-2-one hydrochloride

Palladium black (5g) is added portionwise to a solution of (R)-2-{benzyl-[2-(4-propyl-phenyl)-ethyl]-amino}-1-(4-tert-butoxy-2-isopropoxy-benzothiazol-7-yl)-ethanol (4.00g in formic acid (25 mL) at room temperature. After 1 hour, filtration and evaporation gives the formate salt, which is dissolved in boiling ethyl acetate : MeOH (1 : 1), treated with decolourising charcoal and filtered hot. The solution is allowed to cool, 1M HCl in $Et_2O$ (10

ml) is added and the solvent is removed *in vacuo*. The solid is triturated with ethyl acetate, filtered and dried. MS (ES+) *m/e* 373 ($MH^+$).

Example 7 - 4-hydroxy-7-[(S)-1-hydroxy-2-[2-(4-propyl-phenyl)-ethylamino]-ethyl]-3H-benzothiazol-2-one hydrochloride

The title compound is prepared from (S)-1-(4-tert-butoxy-2-isopropoxy-benzothiazol-7-yl)-2-chloro-ethanol by procedures analogous to those of Preparations 30 and 31 and Example 6. MS (ES+) *m/e* 373 ($MH^+$).

Example 8 - 7-[2-(5,6-diethyl-indan-2-ylamino)-1-hydroxy-ethyl]-4-hydroxy-3H-benzothiazol-2-one

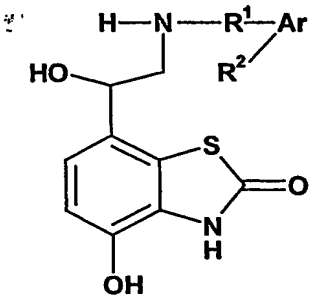
The title compound is prepared from 2-[benzyl-(5,6-diethyl-indan-2-yl)-amino]-N-methoxy-N-methyl-acetamide and (2-tert-butoxy-5-fluoro-phenyl)-thiocarbamic acid O-isopropyl ester by procedures analogous to those of Preparations 10, 11 and 12 and Example 1.
MS (ES+) 399.

Example 9 - 4-hydroxy-7-[(R)-1-hydroxy-2-[2-(3-propyl-phenyl)-ethylamino]-ethyl]-3H-benzothiazol-2-one hydrochloride

The title compound is prepared from (R)-2-{benzyl-[2-(3-propyl-phenyl)-ethyl]-amino}-1-(4-tert-butoxy-2-isopropoxy-benzothiazol-7-yl)-ethanol by a procedure analogous to that of Example 6.

Claims

1. A compound of formula I



I

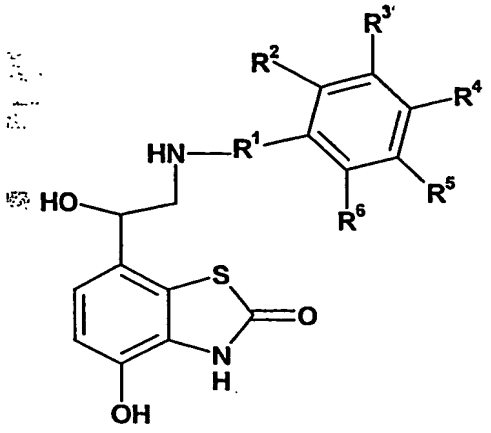
in free or salt or solvate form, where

Ar denotes a phenylene group optionally substituted by one or more substituents selected from halogen, $C_1$-$C_8$-alkyl, $C_1$-$C_8$-alkoxy, $C_1$-$C_8$-alkoxy-$C_1$-$C_8$-alkyl, or $C_1$-$C_8$-alkoxy substituted by phenyl, $C_1$-$C_8$-alkyl-substituted phenyl or by $C_1$-$C_8$-alkoxy-substituted phenyl, $R^1$ and $R^2$ are attached to adjacent carbon atoms in Ar, and

either $R^1$ is $C_1$-$C_8$-alkylene and $R^2$ is hydrogen, $C_1$-$C_8$-alkyl, $C_1$-$C_8$-alkoxy or halogen or $R^1$ and $R^2$ together with the carbon atoms in Ar to which they are attached denote a 5-, 6- or 7-membered cycloaliphatic ring.

2. A compound according to claim 1, in which Ar is phenylene which is unsubstituted or substituted by one or two substituents selected from $C_1$-$C_4$-alkyl, $C_1$-$C_4$-alkoxy, or $C_1$-$C_4$-alkoxy substituted by phenyl, and either $R^1$ is $C_2$-$C_4$-alkylene and $R^2$ is hydrogen or $R^1$ and $R^2$ together with the carbon atoms to which they are attached in Ar denote a 5-membered cycloaliphatic ring.

3. A compound according to claim 1, which is of formula



II

in free or salt or solvate form, where $R^1$ is $C_2$-$C_4$-alkylene and $R^2$ is hydrogen, or $R^1$ and $R^2$ together with the carbon atoms to which they are attached on the indicated benzene ring denote a 5-membered cycloaliphatic ring, $R^3$ and $R^6$ are each hydrogen, $R^4$ is hydrogen, $C_1$-$C_4$-alkyl, $C_1$-$C_4$-alkoxy or $C_1$-$C_4$-alkoxy substituted by phenyl and $R^5$ is hydrogen or $C_1$-$C_4$-alkyl.

4. A compound according to claim 3, in which $R^1$ is $C_2$-$C_3$-alkylene, $R^2$, $R^3$, $R^5$ and $R^6$ are each hydrogen, and $R^4$ is $C_1$-$C_4$-alkyl, $C_1$-$C_4$-alkoxy or $C_1$-$C_4$-alkoxy substituted by phenyl, or in which $R^1$ and $R^2$ together with the carbon atoms to which they are attached on the indicated benzene ring denote a cyclopentyl group fused to the benzene ring, $R^3$ and $R^6$ are each hydrogen and $R^4$ amd $R^5$ are each independently hydrogen or $C_1$-$C_4$-alkyl.

5. A compound according to claim 1, substantially as described in any one of the foregoing Examples.

6. A compound according to any one of claims 1 to 5 for use as a pharmaceutical.

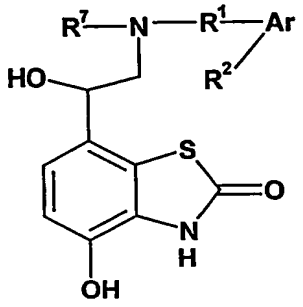
7. A pharmaceutical composition comprising as active ingredient a compound according to any one of claims 1 to 5, optionally together with a pharmaceutically acceptable diluent or carrier therefor.

8. Use of a compound according to any one of claims 1 to 5 for the manufacture of a medicament for the the treatment of a condition which is prevented or alleviated by activation of the β2-adrenoreceptor.

9. Use of a compound according to any one of claims 1 to 5 for the manufacture of a medicament for the the treatment of an obstructive or inflammatory airways disease.

10. A process for the preparation of a compound of formula I in free or salt or solvate form which comprises

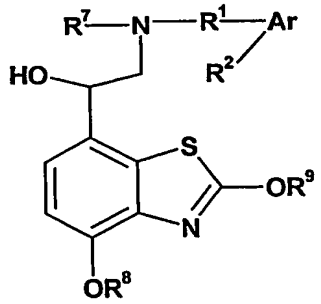
(i) either (A) reacting a compound of formula III




III

where Ar, $R^1$ and $R^2$ are as hereinbefore defined and $R^7$ denotes a protecting group, to replace $R^7$ by hydrogen or

(B) reacting a compound of formula IV




IV

where $R^1$, $R^2$ and $R^7$ are as hereinbefore defined and $R^8$ and $R^9$ each independently denote a protecting group, to convert groups $R^7$, $R^8$ and $R^9$ to hydrogen ; and

(ii) recovering the compound of formula I in free or salt or solvate form.